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Final Report

Synthesis of Compounds of Value in Studying the Mechanism of the Action
of Inhibitors which Prevent Hydrogen Embrittlement of Carbon Steels
Resulting from Acid Pickling

January 1, 1956 to November 30, 1960

Contract No. DA-30-069-ORD-1689

Placed by New York Ordnance District
For the Paint and Chemical Research Laboratory
Aberdeen Proving Ground
Aberdeen, Maryland

Contractor: The Trustees of Rutgers, The State University
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New Brunswick, New Jersey

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Report Prepared

by

Dr. D. B. Denney

and

Joseph Rosen

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DEPARTMENT
ARMY
WASHINGTON
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Foreword

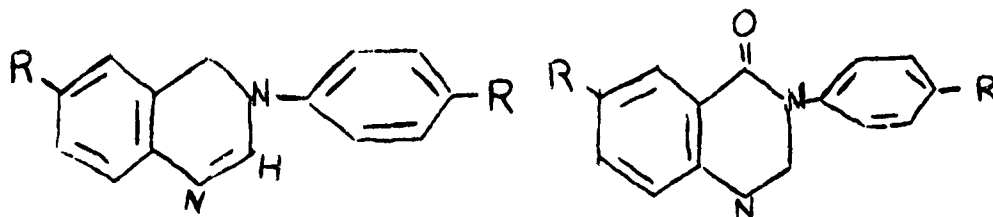
This project has operated in conjunction with the project designated as DA-30-069-ORD-1680. Its purpose has been to prepare organic materials needed in the study of the action of inhibitors of hydrogen embrittlement of carbon steels resulting from acid pickling carried out on DA-30-069-ORD-1680.

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Introduction

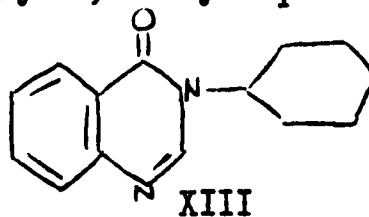
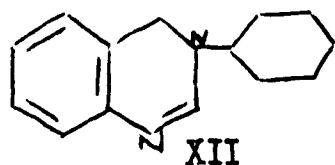
The purpose of this project has been to prepare organic material for testing on DA-30-069-ORD-1680. The compounds synthesized embody the phenylquinazoline and the phenylquinazolone nuclei:



The following compounds were prepared:

	<u>Quinazoline</u>	<u>Quinazolone</u>
R = H	XI	II
R = N(CH ₃) ₂	V	IX
R = OC ₂ H ₅	I	---
R = C ₂ H ₅	IV	---
R = NO ₂	III	---
R = OCH ₃	---	VII
R = Cl	---	VI
R = Br	---	VIII
R = CH ₃	---	X

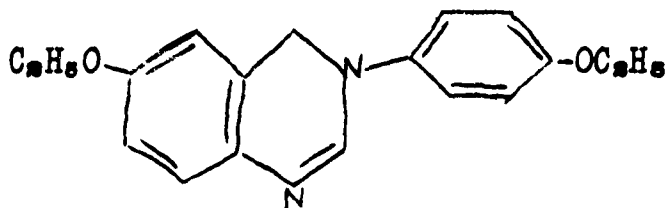
An attempted synthesis of 3-cyclohexyl-3,4-dihydroquinazoline XII:



gave XII which soon decomposed to XIII, the corresponding quinazolone. However, the experimental procedure for this synthesis is included as it is felt that the hydrochloride salt of XII will be obtained if the synthesis is conducted with utmost caution.

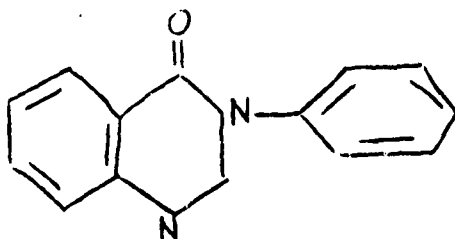
Description of Syntheses

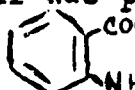
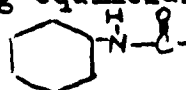
I. 6-ethoxy-3(p-ethoxy phenyl)-3,4-dihydroquinazoline



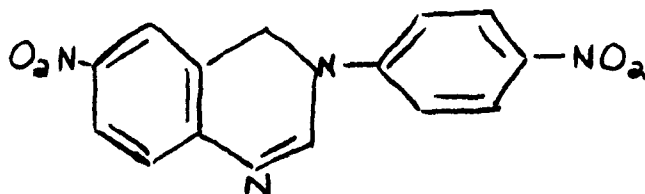
I was prepared from p-phenetidine, formic acid, and formaldehyde, using the method of Wagner, J. Org. Chem. 2, 164 (1937). The melting point of the compound which is recrystallized from ligroin is 137-139°.

II 3-phenyl, 3,4-dihydroquinazolone-4



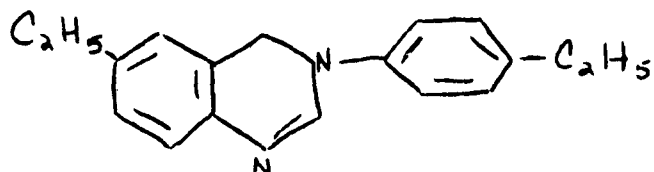
II was prepared by heating equimolar quantities of anthranilic Acid  and formanilide  for ten hours at 128°C. Crystals melting at 135-137° were obtained from dilute ethanol. Reference - C.F. Koelsch JACS 67, 1718 (1945).

III 6-nitro-3-p-nitrophenyl-3,4-dihydroquinazoline



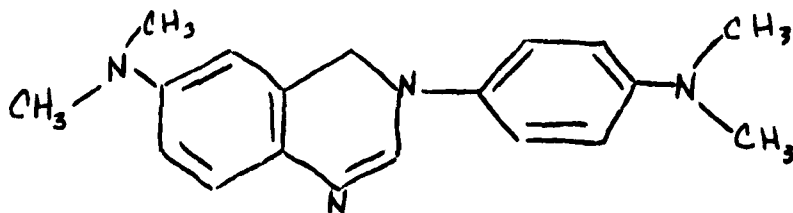
Melting point $243^{\circ} - 246^{\circ}$ was prepared exactly as described in Meyer and Stillich Ber. 35 740 (1902). It should be pointed out that Meyer and Stillich assigned the wrong structure to the compound they obtained, but if one follows their procedure he will obtain III.

IV 6-ethyl-3-p-ethyl phenyl-3,4-dihydroquinazoline

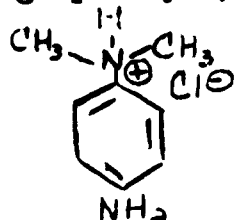


First, mole to mole quantities of sulfuric acid and p-ethyl aniline $C_2H_5-C_6H_4-NH_2$ were reacted in cold ether ethanol solution to form a precipitate of the p-ethylphenylanilinium sulfate salt. One hundred ten gms. 0.5 mole of this salt were reacted with 0.5 moles of formaldehyde (41 ml. of 37% solution) until a solid precipitate formed. Then 1.25 moles (47.2 ml.) of 80% formic acid was added and the mixture was heated in a steam bath for 17 hours. It was made basic with NaOH and steam distilled to remove unreacted p-ethylaniline. The mixture in the distilling flask was cooled and extracted with cold water and then partially evaporated. On cooling, 20 gms. of crude product separated. The product was then recrystallized from methanol, m.p. $110-111^{\circ}$ under nitrogen.

V 3-(p-N,N-dimethylamino phenyl) 6-N,N-dimethylamino-3,4-dihydroquinazoline



The apparatus used was flushed with nitrogen at several intervals during the course of the reaction to lessen the chance of oxidation of the product. 100 gms. (0.58 mole) of Eastman Kodak 492 high purity N,N-dimethyl p-phenylene-diamine mono hydrochloride



was placed in a 3 neck reaction vessel equipped with an automatic stirrer. 45.5 gms. of a 37% formaldehyde solution (0.58 mole) was added slowly through a dropping funnel. A small amount of heat was supplied from a steam bath to initiate the reaction. After the material turned from dark brown to red, 67.5 g of 90% formic acid (1.32 moles) was added dropwise with stirring. The mixture was heated at low heat on steam bath for several hours. The reaction mixture was then made strongly basic with 3N NaOH and steam distilled until the more volatile amines were removed. The remaining solid was dissolved and crystallized from a mixture of acetone and ethyl acetate. m.p. (under nitrogen) 175.5-178.

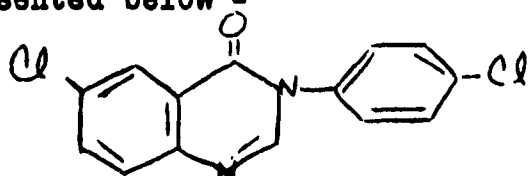
The following compounds

3-p-chloro-6-chloro-3,4-dihydroquinazalone-4	VI
3-p-methoxy-6-methoxy-3,4-dihydroquinazalone-4	VII
3-p-bromo-6-bromo-3,4-dihydroquinazalone-4	VIII

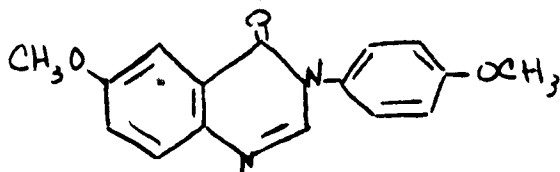
were prepared by dissolving the corresponding quinazolines in acetone, oxidizing with KMnO_4 , and precipitating with NaHSO_3 .

3-p-N,N-dimethylamino 6-N,N-dimethylamino 3,4-dihydroquinazalone-4, (IX), was prepared by dissolving V in acetone, adding 2 drops of Nuodex and refluxing while bubbling oxygen through the solution. Then activated charcoal was added, the solution was filtered and cooled and the product was recrystallized from dilute ethanol. The melting points

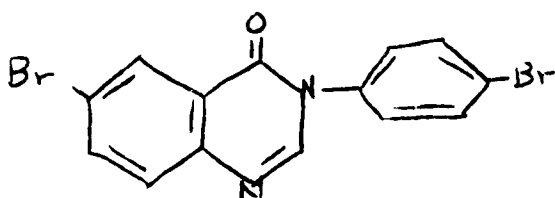
are presented below -



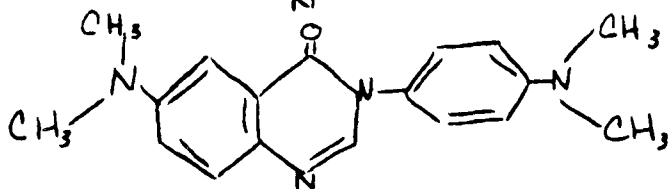
224. - 224.5



191.5 - 192.5

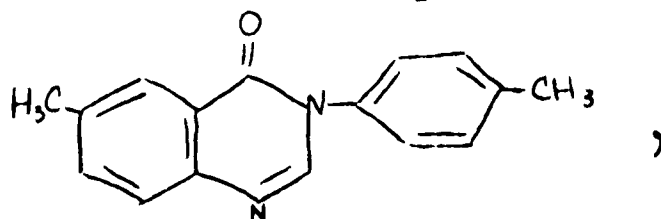


183 - 188



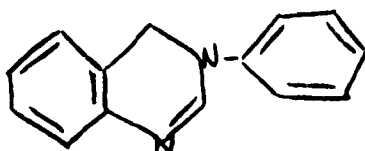
256 - 257

X 3-p-tolyl-6-methyl-3,4-dihydroquinazolin-2(1H)-one,

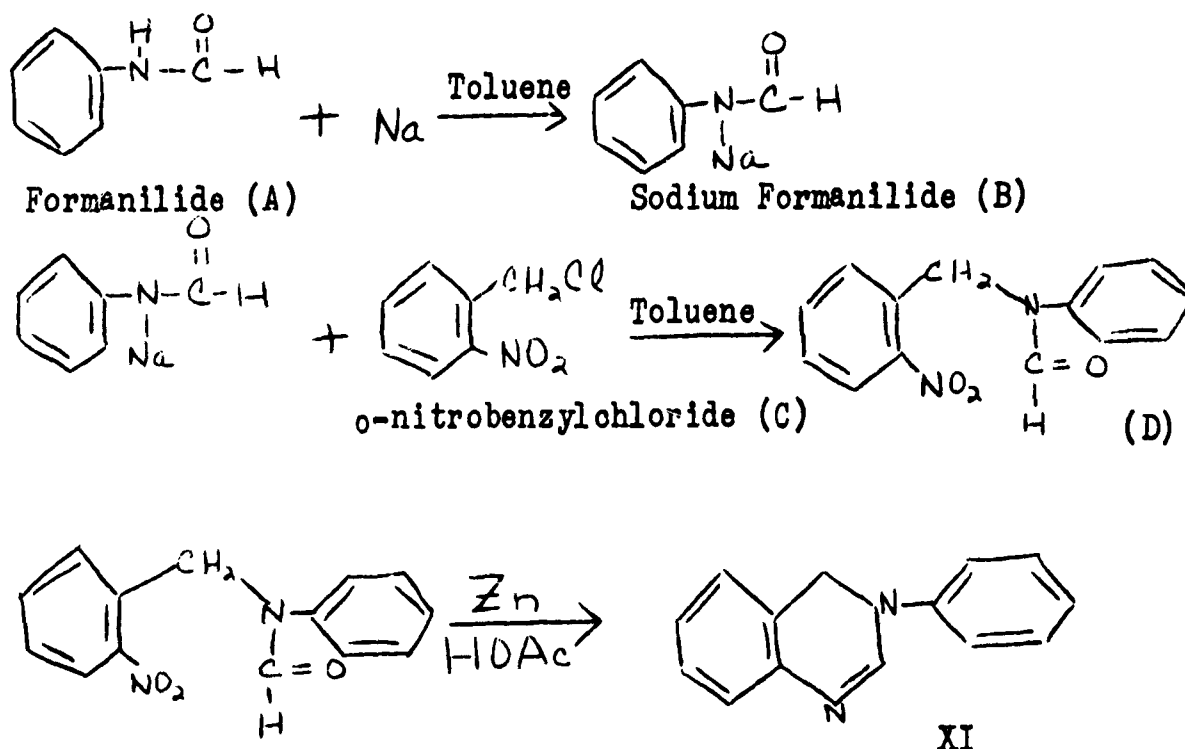


was prepared by placing 3-p-tolyl-6-methyl-3,4-dihydroquinazoline, (DHQ), in a 110° oven until portions of the gummy mass when dissolved in HCl no longer showed UV peaks at 238 mμ. The gum was dissolved in absolute ethanol, and crystallized by adding a large amount of petroleum ether and then placing the solution in a freezer. Recrystallization from absolute ethanol gave crystals melting at 113.5 - 114.5°C. Yield 50%.

XI 3-phenyl-3,4-dihydroquinazoline,



, was prepared using methods adapted from Paul and Busch, Ben 22b 2685 (1889). The overall scheme is:



N-phenyl o-nitrobenzyl formamide (D)

1. Preparation of (B).

To a 2 l. three-neck flask equipped with stirrer and condenser, 800 ml. of dry toluene and 19 gms. (0.86 mole) of sodium were added. The mixture was heated on a steam bath until the Na melted. To this, a toluene solution of 100 gms. (0.82 mole) (A) was added very slowly.

The white, finely divided precipitate which settled out was (B).

2. Preparation of (D).

To the reaction mixture above, a solution of 140 gms. (0.82 mole) of (C) in 500 ml. dry toluene was added slowly. Water was then added to remove the NaCl. The toluene layer was then steam distilled to remove the toluene, and a dark brown oily residue remained in the distillation flask. This was separated from the water and was crystallized by adding 20 ml. of ether-alcohol and allowing to stand overnight in a freezer. Yellow crystals from CS_2 melted at $76.5^\circ C$. Yield 20%.

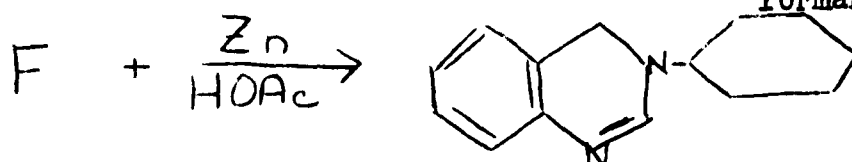
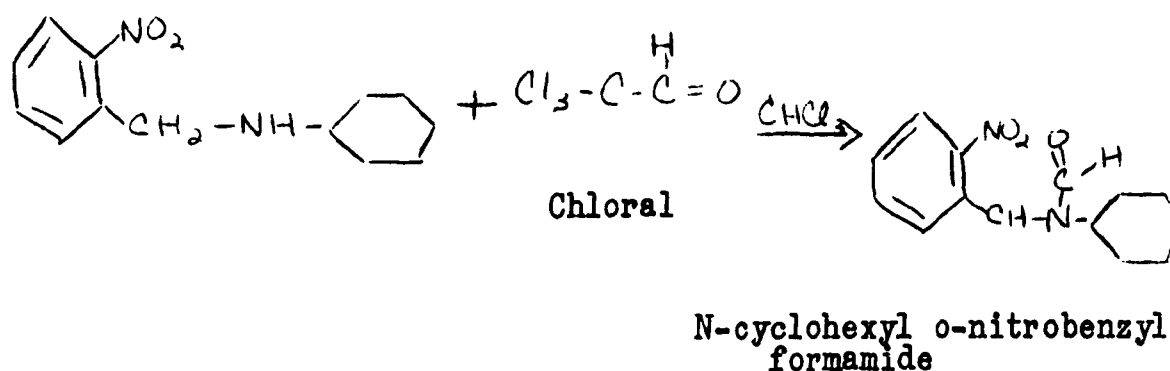
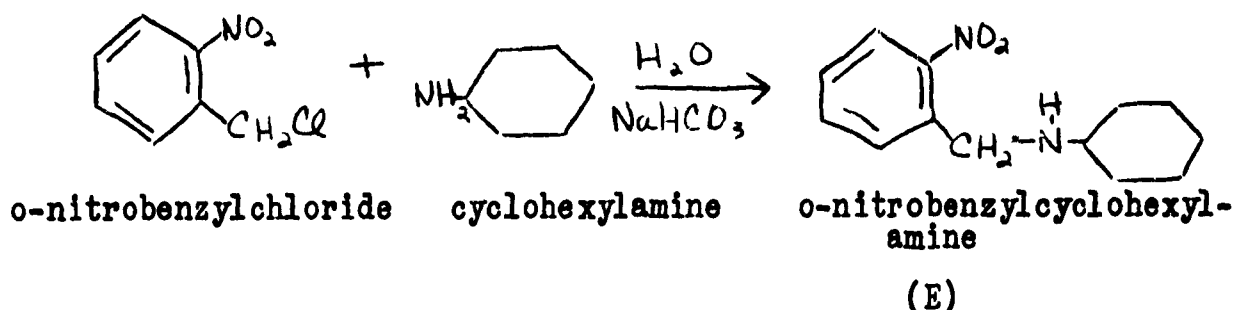
3. Reduction and cyclization of (D) to XI.

13.5 gms. (D) were dissolved in 250 ml. glacial acetic acid. Thirty five gms. of zinc dust were then added slowly and the reaction mixture was stirred until it cooled to room temperature. The reaction mixture was then filtered; the residue was washed with hot acetic acid; and the combined filtrates were neutralized with concentrated NH_4OH . The slightly alkaline solution was then extracted with ether, and the extract was dried over Na_2SO_4 . The ether was then evaporated and the product recrystallized from ether. m.p. (under N_2) 95° .

XII 3-cyclohexyl-3,4-dihydroquinazoline

This compound was prepared but due to its instability, we were never able to determine its physical properties. However, because it is felt that this compound is of extreme importance and that its hydrochloride salt can be prepared if the proper precautions are taken, a description of the synthetic procedure is presented.

The overall scheme follows:



1. Preparation of E

In a three-neck 1-liter flask equipped with reflux condenser and mechanical stirrer were placed 148.5 gms. cyclohexylamine (1.5 mole, 31.5 gms. NaHCO₃ (0.375 mole) and 100 ml. H₂O. The mixture was heated on a steam bath and 64.3 gms. (0.375 mole) o-nitrobenzylchloride was added over a period of one and a half hours. The flask was then heated for an additional three and a half hours. The oily layer was separated from the aqueous layer, dried over MgSO₄ and filtered. It was then

distilled under vacuum at room temperature through an air cooled condenser. The unreacted cyclohexylamine comes off at this point. The remaining brown oil is taken up in dry ether and reacted with HCl gas at 0°. The hydrochloride salt of (E) is recrystallized from iso-propyl alcohol and melts at 223°C. (E) is then liberated with a solution of Na₂CO₃ and extracted with hexane. After the hexane is removed, there remains a yellow non-viscous oil (E) which decomposes at its atmospheric boiling point. Yield 35%.

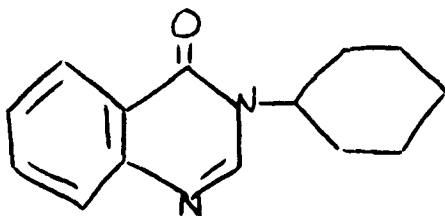
2. Preparation of (F)

Eleven gms. of (E) were dissolved in 50 ml. of dry chloroform and 6.8 gms. of chloral $\text{Cl}_3\text{-C}-\overset{\text{O}}{\underset{\text{H}}{\text{C}}}\text{-H}$ were added dropwise with stirring under dry conditions. The mixture was refluxed for 24 hrs., and then the chloroform was boiled off. A heavy oil, which crystallized upon addition of a few drops of ether resulted. The crystals were recrystallized from EtOH-H₂O (a better solvent should be found) and melted at 89° - 91°. Yield 86%.

3. Attempted Preparation of XII

The same procedure was used here as in the preparation of 3-phenyl-3,4-dihydroquinazoline, except that the neutralization with NH₄OH was carried out under N₂. From this point on the procedure was again the same except that the compound was kept under nitrogen in further manipulations. An infra-red analysis of the crystals obtained gave overwhelming evidence that XII had indeed been synthesized, but further work was thwarted by the observation that the crystalline compound was rapidly becoming oily. An infra-red spectrum of the oil showed a large carbonyl peak, leading us to conclude that XII is

completely unstable in air at room temperature and is converted to its quinazolone,



XIII

From an examination of the structure of XII it is apparent that its hydrochloride will not be as easily oxidized. If one were to carry out this preparation in a dry box filled with N_2 and were to treat the ether solution of XII with gaseous HCl, he would most likely be able to isolate $XII \cdot HCl^{\oplus \ominus}$.

Identification of Technicians

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